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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,996	12/30/1999	JOHANNES CHRISTIANUS VAN GROENINGHEN	49477(1958)	3246

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EXAMINER	
ANDRES, JANET L	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/446,996	VAN GROENINGHEN, JOHANNES CHRISTIANUS	
	Examiner	Art Unit	
	Janet L Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO AMENDMENT

1. Applicant's amendment filed 25 January 2002 is acknowledged. Claims 1-9, 12, and new clams 14-17 are pending in this application. Claims 1-9 and 12 are withdrawn from consideration as drawn to a non-elected invention. New claims 14-17 are examined in light of Applicant's species election of GnRH agonists. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

2. The objection to the drawings is withdrawn in response to Applicant's submission of new drawings. The corrected or substitute drawings were received on 25 January 2002. These drawings are approved.

3. The rejection of the claims under 35 U.S.C. 101 as drawn to non-statutory subject matter is withdrawn in response to Applicant's submission of new method claims.

4. The rejection of the claims under 35 U.S.C. 112, second paragraph, as indefinite in the recitation of "agonist" is withdrawn in response to Applicant's arguments.

Claim Rejections/Objections Maintained/New Grounds of Rejection

5. The objection to the specification is maintained. The trademarks present in the specification have not been capitalized, as required by MPEP §608.01(v). Applicants indicate that a replacement specification will be submitted. The objection is maintained of record until the substitute is received. The Examiner notes additionally that compounds described as antagonists in Table 1 are referred to as agonists on p. 10, line 3. Clarification is required.

6. The rejection of claims 10, 11, and 13 under 35 U.S.C. 112, first paragraph, is maintained with respect to new claims 14-17.

Applicant argues that the specification describes and enables Applicant's invention. Applicant points to page 8, lines 3-24 as describing the invention and its advantages over the prior art. Applicant additionally points to table I as providing a list of suitable GnRH agonists and antagonists. Applicant further points to a preferred treatment protocol on page 11, as well as the Examples beginning on page 17. Applicant further notes that extensive experimentation is permissible if it is merely routine and the specification provides a reasonable amount of guidance. Applicant argues that clinical trial data are not required. Applicant states that sufficient reasons have not been presented to establish why one skilled in the art could not use the invention, and states that such a rejection is improper. Applicant argues that "in absence of any evidence why a supporting disclosure is not sufficient, the mere allegation of inadequacy is not considered to constitute a satisfactory basis for rejection" and cites *In re Marzocchi.*

Applicant's arguments have been fully considered but have not been found to be persuasive.

What is provided on page 8 is a list of conditions that Applicant contemplates treating with GnRH agonists or antagonists, the indication that the blood-brain barrier is not relevant for these tumors, and the statement that GnRH crosses the blood-brain barrier. Table I is, as Applicant indicates, a list of GnRH agonists and antagonists. The protocol beginning on page 11 states that "no clinical criteria for exclusion exist" (p. 12, lines 4-5) and indicates only that " a suitable ligand (GnRH agonist, GnRH antagonist or conjugates) is selected and administered" (lines 14-15) and that "the treatment is continued as long as no complete remission has occurred". As stated in the previous Office Action, Applicant's *in vivo* examples are proposed studies. Thus what is provided is a list of drugs, a general protocol, and a set of proposed

experiments. As stated previously, there is no guidance to indicate that these receptors are present all of cancers Applicant's methods are intended to treat, there is no guidance as to what level of receptor would be predictive of a favorable response, and there is no indication as to what level of inhibition would be required or could be obtained.

What Applicant has provided is three *in vitro* experiments indicating that 15-35% inhibition of proliferation could be obtained in a cell line using a GnRH agonist, a GnRH antagonist, or LHRH, and evidence of widely varying GnRH receptor levels in some tumor samples. This variation is observed in tumors of the same type as well as in different tumor types. While clinical trial data are not required, what is required is sufficient evidence or guidance to allow one of skill in the art to make and use the invention without undue experimentation. As discussed in the previous office action, the art teaches that tumorogenesis is a complicated process involving many factors. Limited *in vitro* data such as that provided in the instant Application are not predictive of anti-cancer activity. Shi et al. (J. Chem. Inf. Comput. Sci., 2000, vol. 40, pages 367-379), investigating results from the NCI Anticancer Drug discovery Program, which uses 60 cell lines, states "the growth inhibitory activity for a single cell line is not very informative" (p. 368). Johnson et al. (Brit. J. Cancer, 2001, vol. 84, pages 1424-1431) states on p. 1424 that selection based on potency, activity against a particular disease category, and/or activity against a few specific cell lines generated a large number of candidates and an additional screen was required to identify candidates for further preclinical development (p. 1424). *In vitro* screening is merely the first step in a three-part protocol. Thus, the art teaches that the experimentation required to identify and use an agent identified solely by limited *in vitro* data is <u>not</u> routine. Further, as stated previously, the claims encompass all GnRH agonists,

including those not yet known. Also as stated previously, the efficacy of a given compound is dependent on many variables including pharmacological, physiological, and biochemical factors. Applicant's teachings, which show only an effect of one compound on one cell type, and in fact show a greater effect from an antagonist, are not sufficient to allow one of skill in the art to determine which of the agonists potentially encompassed would function as claimed.

Applicant further argues that the rejection is improper and that sufficient reasons have not been provided as to why the artisan could not use Applicant's invention, and cites *In re Marzocchi*. Neither the truth nor the accuracy of Applicant's disclosure is doubted; what is stated above and in the previous Office Action is that the disclosure is not sufficient to support the claimed invention. As explained in detail above and previously, the claims are broadly drawn, the art is unpredictable, and Applicant's own observations indicate that receptor levels and the effects of agonists and antagonists are variable. The specification provides no guidance as to what level of receptor expression is required or would be expected, or what level of inhibition is required or could be expected, or as to whether an agonist or an antagonist should be used. Further, the art generally teaches that the experimentation required to proceed from limited *in vitro* data to a method of treatment is extensive and not routine. Thus, there is insufficient guidance in the specification to allow the skilled artisan to use Applicant's invention with an expectation of success. Without guidance to allow such a prediction of success, it would require undue experimentation for the skilled artisan to use Applicant's invention.

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly

signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
April 19, 2002

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER